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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,441	12/20/2001	Stephen Quirk	1443.024US1	2667
21186	7590	08/23/2004	EXAMINER	
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A. P.O. BOX 2938 MINNEAPOLIS, MN 55402			KISHORE, GOILAMUDIS	
			ART UNIT	PAPER NUMBER
			1615	
DATE MAILED: 08/23/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/027,441

Applicant(s)

QUIRK, STEPHEN

Examiner

Gollamudi S Kishore, Ph.D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 16-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The response dated 4-30-04 is acknowledged.

Claims included in the prosecution are 1-15. Claims 16-27 remain withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner (4,925,673) in combination Mathiowitz (5,271,961) and Margolin (6,541,606).

Steiner discloses protenoid delivery systems of thermally condensed amino acids (abstract and examples). What is lacking in Steiner is the teaching of further cross-linking using disulfide bridges.

Mathiowitz while disclosing protein microspheres teaches that the microspheres can be modified for a given application chemically to produce a protein having enhanced or altered thermal stability, surface reactivity and others; one such modification suggested by Mathiowitz is cross-linking of the protein using agents such as glutaraldehyde (abstract, col. 5, lines 50-57; col. 6, lines 54-62). Mathiowitz however, does not teach disulfide cross-linking agents.

Margolin while disclosing stabilized protein formulations teaches cross-linking of the proteins using several chemical agents including aldehydes and thio-labile linkers having the structure $R'-S-S-R$. According to Margolin, thio-labile cross-linkers are reversible cross-linkers and several disulfide cross-linkers are known and commercially available. (abstract, col. 24, line 29 through col. 26, line 61).

It would have been obvious to further modify the protenoids of Steiner introducing dithio linkages since Mathiowitz teaches that the protein microspheres can be modified for a given application and cross-linked using aldehydes such as glutaraldehyde and Margolin teaches that the equivalency between aldehyde cross-linking and thio-labile cross-linking. One of ordinary skill in the art would be further motivated to used thio linkage in view of Margolin's teachings of reversibility of thio linkages.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the references fail or teach all the claimed elements and that the combination of references fails to teach reversible cross-linking groups on proteinoid microspheres that are made of amino acids where drug release can be triggered by the opening of a reversible cross-linking group on the microsphere. Applicant also argues that the combination of references fail teach that such a reversible cross-link can be removed under physiological conditions (i.e., in serum as described in the present application at page 25), without direct intervention by addition of another reagent, such as a an H_2 catalyst or a hydride. The examiner disagrees. The reference of Margolin

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particularly teaches on col. 24, lines 41-45 that the bond can be broken by altering one or more conditions in the surrounding environment such as pH, temperature or thermodynamic water activity.

Applicant argues that Steiner is limited to disclosure of proteinoid microspheres that are not cross-linked. The examiner agrees and points out that the motivation to further cross-link the thermally condensed amino acids can be derived from the secondary references. Applicant argues that Mathiowitz is limited to disclosure of methods for making protein microspheres by mixing a solution of proteins and not amino acids. This argument is not found to be persuasive since thermally condensed amino acids are also proteins and the method of cross-linking proteins (or proteinoids) would be the same irrespective of the method by which they are produced. Applicant argues that Margolin discloses methods for stabilizing biologically active macromolecules by crystallizing them from aqueous solutions using evaporation and Margolin provides no mention or teaching of proteinoid microspheres. This argument is not found to be persuasive since Margolin is combined for its teachings of the reversible cross-linking of proteins using the claimed disulfide cross-linkers. The examiner disagrees with Margolin that Margolin does not teach proteinoid microspheres at all since encapsulation of the protein crystals in polymeric carriers such as albumin is evident from col. 27 line 45 through col. 28, line 60. Applicant's arguments that one of ordinary skill in the art would not have a reasonable expectation of finding the present invention from the combination because none of the references teach that disulfide linker can be cleaved in

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human serum are not persuasive since from Margolin's teachings as pointed out above, that the bond can be broken by altering one or more conditions in the surrounding environment such as pH and temperature; one of ordinary skill in the art would therefore, would be motivated to use disulfide cross-linkers with a reasonable expectation of success.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM-4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602.

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The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK